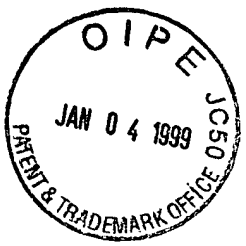

183

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#36
Appeal
1/8/99

Appellants: John P. Atkinson, Dennis Hourcade, and Malgorzata Krych

Serial No: 08/126,505 Art Unit: 1646

Filing date: September 24, 1993 Examiner: L. Spector

For: MODIFIED CR1 ANALOGUES

Assistant Commissioner of Patents
Washington, D.C. 20231

REVISED APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1, 3-5, 8-16, 18-20, 23-32 and 34 in the Office Action mailed November 5, 1997 in the above-identified patent application, revised in response to the Advisory Action mailed December 4, 1998, stating that the previously submitted Appeal Brief did not address rejections under 35 U.S.C. §112, second paragraph. A Notice of Appeal was mailed on May 5, 1998. A Petition for an Extension of Time for two months and the appropriate fees for the filing of this Appellants' Brief and the Extension of Time were enclosed with the Appeal Brief mailed September 8, 1998.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Washington University, St. Louis, MO, and its licensee, Cytomed, Inc., Cambridge, MA, and its corporate partner, Chiron Corporation, Emeryville, CA.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1, 3-5, 8-16, 18-20, 23-32, and 34 are pending. Claims 4, 5, 10, 11, 14, 19-20, 25, 26, 29 and 34 have been withdrawn from consideration. Claims 1, 3, 8, 9, 12, 13, 15, 16, 18, 23, 24, 27, 28, and 30-32 are on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed July 28, 1997. These claims are attached in Appendix I.

An amendment to remove rejections under 35 U.S.C. §112was mailed September 8, 1998. The claims as proposed to be amended in response to the rejections under 35 U.S.C. §112 are attached in Appendix II. The Examiner refused to enter the Amendment in the Advisory Actions mailed October 20, 1998, and December 4, 1998. A Petition requesting entry of the Amendment was mailed November 20, 1998. No decision has been received on the Petition.

(5) SUMMARY OF THE INVENTION

The invention defined by the claims on appeal are chimeric proteins which contain one or more short consensus repeats (SCRs) from more than one complement regulatory (RCA) protein, modifications of RCA recombinants in which SCRs are arranged in different orders, and truncated versions of RCA proteins containing as few three SCRs (page 9, lines 20-31). The modified proteins retain complement inhibitory activity, which may be altered in specificity, affinity, or mechanism (page 9, lines 29-31). Additional properties may be conferred on the chimeric proteins (page 13).

(6) ISSUES ON APPEAL

The issues presented on appeal is whether claims 1, 3, 12, 13, 15, 16, 18, 27, 28, 30, 31, and 32 are non-obvious under 35 U.S.C. §103 over Lowell, et al., J. Exp. Med. 170, 1931-1946 (1989) in combination with U.S. patent No. 5,256,642 to Fearon, et al., WO 89/01041 by Caras, et al., Atkinson, et al. Immunol. Today 8, 212-215 (1987) and U.S. Patent No. 4,935,233 to Bell, et al.; and whether claims 8, 9, 10, 23, 24, and 25 were indefinite under 35 U.S.C. §112, paragraph 2.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims are of different scope, and include both methods and compositions, requiring a different analysis of the art. Claims 8, 9, 10, 23, 24, and 25 also include language which the examiner has objected to not on prior art grounds, but

which is drawn to very specific amino acid substitutions.

The claims on appeal are those drawn generally to chimeric proteins of two complement regulatory proteins which are formed of short consensus repeats (SCRs) (complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H), wherein the chimeric protein includes as few as three SCRs, and which binds to the complement proteins C3b, C4b, or both C3b and C4b. This is the subject matter of claim 1, although the specific combination of CR1 and CR2 is excluded. Claims 16 and 27 are methods for making the analog. Claims 31 and 32 are drawn to a DNA molecule encoding the analog.

Claim 3 defines the protein used to form the chimeric protein as CR1. Claim 18 is a method of making the analog.

Claim 12 is drawn to the analog of claim 1 wherein the analog includes SCRs from at least two of the complement regulatory proteins.

Claim 13 is drawn to the analog which includes SCRs 2, 3, and 4 of DAF and has C3b cofactor activity, C4b cofactor activity, and decay accelerating activity. Claim 28 is a method for making the analog.

Claims 3, 12, and 13 all require different compositions.

Claim 15 is drawn to a pharmaceutical composition. Claim 30 is a method for making a pharmaceutical composition.

Claims 8, 9, 10, 23, 24, and 25 are drawn to specific compositions at which certain amino

acids can be substituted.

(8) ARGUMENTS

(i) Background and The Invention

The Complement System

The complement system is regulated via a number of interrelated mechanisms. There are two general mechanisms for inhibition of the destructive components of the complement system, which may be desirable due to autoimmune disease, transplant rejection, or other diseases such as septic shock. The first mechanism is generally reversible, facilitating the dissociation of the C3 convertases--i.e., C3b from Bb and C4b from C2a. Facilitation of dissociation is sometimes known as decay acceleration. The dissociation may also involve reversible binding of the antagonist proteins to C3b or C4b components, thus preventing their reassociation. The other mechanism, which is an irreversible inactivation process, results from proteolytic cleavage of the C3 convertase components C3b or C4b by the serine protease factor I. This proteolytic cleavage occurs only in the presence of a cofactor. Both general regulatory mechanisms, the facilitation of dissociation of C3b and C4b and the inactivation of C3b and C4b through cleavage by factor I, also apply to the inhibition of the alternative pathway C5 convertase (C3bBbC3b) and the classical pathway C5 convertase (C4bC2aC3b).

The reversible binding to C4b or C3b to dissociate the C3 convertases is effected by two plasma proteins designated C4 binding protein (C4bp) and factor H, and by two membrane

proteins designated decay acceleration factor (DAF) and complement receptor 1 (CR1). Reversible binding to C4b is effected by C4bp, DAF and CR1 while reversible binding to C3b is effected by factor H, DAF and CR1.

There is considerable uniformity among the RCA family of proteins. All of them are composed of 60-70 amino acid repeating units commonly designated "short consensus repeats" (SCRs). Each SCR shares a number of invariant or highly conserved amino acid residues with other SCRs in the same protein or SCRs in other family members. Those members of the family which are membrane bound also have at their C termini either transmembrane regions and intracellular regions or a glycolipid anchor. CR1 contains 30 SCR, followed by transmembrane and cytoplasmic regions. CR2 contains 16 SCR, followed by transmembrane and cytoplasmic regions. DAF and MCP each contain four SCR, followed by glycolipid anchor regions. The C4 binding protein is a more complex protein, having seven alpha subunits and one beta subunit. The alpha subunit consists of eight SCR and the beta subunit consists of three SCR. Factor H consists of twenty SCR.

The Claimed Invention

The claims encompass chimeric proteins derived from these complement regulatory proteins which include SCRs from other related proteins, wherein the SCRs have been rearranged, and truncated forms of these proteins which include as few as three SCRs. In some embodiments, modifications are made using corresponding SCRs of the protein as sites for alteration. By "corresponding SCR" is meant the most highly homologous SCR as judged by

the amino acid sequences of the protein. Exon structure can in some cases facilitate this assignment. SCRs 1-3 of CR1 correspond to SCRs 2-4 of DAF. SCRs 1-3 of factor H, CR1, C4bp and MCP are corresponding sequences among these proteins. CR1 is organized into a series of long homologous repeats (LHRS) containing 7 SCRs so that CR1 SCRs 1-7 correspond to CR1 SCRs 8-14; 15-21; and 22-28. CR2 is organized into a series of long homologous repeats of 4 SCRs in length. SCRs 1-2 of CR1 correspond to SCRs 3-4, SCRs 7-8, SCRs 11-12 and SCRs 15-16 of CR2.

These proteins are characterized by C4b-binding activity, C3b-binding activity, C4b cofactor activity, and/or C3b cofactor activity. In general, it takes two to three SCRs for each activity. Activities which are biologically important include decay acceleration or dissociation, C3b cofactor activity and C4b cofactor activity. Cofactor activity requires binding but binding alone may not be sufficient for cofactor activity.

It is generally accepted that CR1 C4b binding and cofactor activity requires SCRs 1, 2 and 3, 8, 9, and 10, or 15, 16, and 17, which are corresponding regions of the protein. C3b binding and cofactor activity requires SCRs 8, 9, and 10, or 15, 16, and 17, which are corresponding regions of the protein. MCP C4b binding and cofactor activity requires SCRs 1, 2, 3, and 4. MCP C3b binding requires SCRs 3 and 4; cofactor activity requires SCRs 2, 3, and 4. C4b binding and cofactor activity requires SCRs 1, 2, and 3. DAF decay accelerating activity requires SCRs 2, 3, and 4. Factor H C3b binding activity is mediated by the first five SCRs.

What Discoveries?

Based on these discoveries, it is possible to design a more potent soluble complement

Not Claimed

inhibitor by modifying corresponding regions to increase affinity for C4b and C3b or to design soluble complement inhibitors that specifically inhibit one part of the complement system. These modifications can be in the form of specific substitutions of amino acids that alter C3b or C4b binding within corresponding SCRs of CR1 or other RCA proteins, or substitution of SCRs from one protein into another.

The identification of the amino acid sequences essential (or refractory) to binding to C4b and C3b and C4b and C3b cofactor activity permits transposition of similar sequences into corresponding regions of the same protein or corresponding regions of other family members or alteration of sequences which bind C3b and C4b so as to alter their affinities.

In the case of CR1, four corresponding regions of interest are SCRs 1-3, SCRs 8-10, SCRs 15-17 and SCRs 22-24. The SCR portions labeled 2-4 in Figure 2B for DAF correspond to those labeled 1-3, 8-10, 15-17 and 22-24 for CR1 in Figure 2B. Substitution of portions of DAF with homologous CR1 sequences provides forms of DAF with cofactor activity and/or binding activity, such as is exhibited by CR1. Similarly, substitutions of portions of MCP with homologous sequences provides forms of MCP with increased binding affinity and cofactor activity and/or increased dissociation activity.

(ii) Rejections Under 35 U.S.C. § 103

Claims 1, 3, 12, 13, 15, 16, 18, 27, 28, 30, 31, and 32 were rejected under 35 U.S.C. §103 as obvious over Lowell, et al., J. Exp. Med. 170, 1931-1946 (1989) in combination with U.S. patent No. 5,256,642 to Fearon, et al., WO 89/01041 by Caras, et al., Atkinson, et al. Immunol.

Today 8, 212-215 (1987) and U.S. Patent No. 4,935,233 to Bell, et al.

(a) The Legal Requirements of Obviousness

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

a. The prior art does not suggest the claimed invention.

Lowell was trying to determine which regions of CR2 were critical for binding to the protein by the Epstein-Barr virus. As a result, Lowell made constructs that he then tested for binding by virus. Lowell never looks at, nor predicts, that one can alter functional activity (defined as binding to C3b, C4b or C3b and C4b), only viral binding activity (which he refers to as functional activity).

Only appellant rearranged or inserted SCRs from one protein into another protein to look at the effect on binding to C3b, C4b or C3b and C4b, and determined which SCRs were not only responsible for the different activities, but which were homologous in terms of structure and function, and which could be used. Only appellant made truncated complement regulatory proteins and determined that as few as three SCRs were required for activity. The examiner's

conclusions regarding what was, or was not, known at the time regarding these proteins does not make up for this deficiency: it was not known that one could rearrange SCRs or insert "parts" (i.e., SCRs with other activities) from one complement regulatory protein into another and actually transfer an activity from one protein to another. Lowell therefore cannot make obvious the subject of the claims.

The secondary references do not make up for this deficiency. Caras and Fearon disclose that truncated (or soluble, i.e., not including the transmembrane domains, but including in their original order and total number all SCRs) DAF and CR1 can be used as complement inhibitors. No where is there anything suggesting that one could use fewer SCRs, or rearrange the SCRs, or exchange the SCRs between complement regulatory proteins!

Bell merely discloses that one can make chimeric molecules, using proteins such as cytokines, all of which are very short, with no structures resembling SCRs, and with single activities even though binding to different receptors. Bell does not insert "pieces" of one complex, multiactivity protein into the middle of another, much less provide guidance that would lead one skilled in the art of complement proteins to do so.

Therefore none of the secondary references lead one of skill in the art to make that which appellants' claim.

b. A *prima facie* case of obviousness cannot be established by hindsight reconstruction.

The prior art must provide one of ordinary skill in the art with the motivation to make the

proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

The proteins from which the claimed analogs are derived are very large, complex, and in most cases, have mutiple biological activities. One could not have predicted that changing domains within a protein could confer a discrete activity since these are extremely large and complex proteins, and one would predict steric hindrance and other factors to interfer with the transfer of activity. It was as likely that rearranging these highly conserved domains would destroy their activities as it was likely that any one or more activities would be retained. Since Lowell did not screen for functional activity of his constructions, there was no way to predict that even the one construct which inserted CR1 SCRs into CR2 would have activity - only appellants ever actually tested constructs for binding.

unsupported

The examiner has brushed aside these arguments as though such "mixing and matching" was routine, with no evidence that such activities would have been predictable or routine. In fact, it was suspect that even truncation of these complex proteins would not destroy their activities, as is readily apparent from review of Caras and Fearon. What appellants have done

greatly exceeds the disclosures or predictions of the prior art.

(iii) Rejections under 35 U.S.C. §112, second paragraph

Claims 8, 9, 10, 23. 24 and 25, as pending on appeal in Appendix I, define specific amino acid sequences. In certain parts of the sequences, alternative amino acids are described. For example, in claim 24, last line, following a Markush group, the claim states that the list includes sequences with "substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F,V), (K/R), (Q/N), (D/E), and (G/A)". As proposed to be amended, this language would be replaced with "these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G". This amendment does not change the scope of the claim, merely makes even more explicit the meaning of the shorthand alternative expressions "amino acid/amino acid/amino acid", where the amino acids are structurally similar amino acids which can be substituted for each other in the defined sequences. It is believed those skilled in the art can make reference to any biochemistry textbook and determine which amino acids are referred to by the single letters A, D, E, etc. and which are known to be structurally similar. This is explicitly referred to in the application at page 14, lines 17-22.

The standard under 37 C.F.R. §112 is whether one skilled in the art would understand the metes and bounds of the claimed subject matter. It is believed that the terminology used in the

claims is in very common usage among those skilled in the art and would be clearly and unambiguously understood.

(9) SUMMARY

The prior art does not disclose transfer of an activity associated with one or more SCRs of complement regulatory proteins into another protein. The prior art leads one of skill in the art to believe the field was unpredictable and that even as minor a modification as truncation of these proteins by removal of the transmembrane domain could have led to a loss of activity. The one publication cited which discloses transfer of SCRs from one protein, CR1, into a second, CR2, never tested for biological activity, only binding of virus. One skilled in the art could not have predicted that one could transfer activities from one large and complex complement regulatory protein to another with any liklihood of success. Accordingly, the subject matter of claims 1, 3, 12, 13, 15, 16, 18, 27, 28, 30, 31, and 32 is not obvious over Lowell, et al., J. Exp. Med. 170, 1931-1946 (1989) in combination with U.S. patent No. 5,256,642 to Fearon, et al., WO 89/01041 by Caras, et al., Atkinson, et al. Immunol. Today 8, 212-215 (1987) and U.S. Patent No. 4,935,233 to Bell, et al.

The claims are definite to those skilled in the art, as pending on appeal or as proposed to be amended, and therefore comply with 35 U.S.C. §112, second paragraph.

(10) CONCLUSION

Claims 1, 3-5, 8-16, 18-20, 23-32, and 34 should be allowed.

Respectfully submitted,

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Date: December 29, 1998

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jean Hicks

Date: December 29, 1998

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APPENDIX I: CLAIMS ON APPEAL

1. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, and those complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b or C3b and C4b.

3. The analog of claim 1 wherein the protein is complement receptor one.

4. The analog of claim 1 wherein the protein is decay accelerating factor.

5. The analog of claim 1 wherein the protein is factor H.

8. An analog of a protein

selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No:

13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; and substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A).

9. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13 selected from the group consisting of:
79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T (amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino

acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37: S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof.

10. An analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No. 4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof.

11. The analog of claim 1 wherein the complement regulatory protein is factor H

comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

12. The analog of claim 1 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

13. The analog of claim 1 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

14. The analog of claim 1 wherein the region of the protein having biological activity consists of three short consensus regions and has two complement regulatory activities.

15. The analog of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a patient in need thereof.

16. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, comprising

constructing a DNA sequence encoding a protein analog selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived

from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b, or C3b and C4b, and

expressing the DNA sequence in a suitable host for expression of the protein analog.

18. The method of claim 16 wherein the protein used to form the analog is complement receptor one.

19. The method of claim 16 wherein the protein is decay accelerating factor.

20. The method of claim 16 wherein the protein is factor H.

23. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos. 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-

A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A),

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

24. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T (amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37:

S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and combinations thereof,

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

25. A method for making an analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of

180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No. 4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), substitutions with structurally similar amino acids selected from the group consisting of (I,L,V), (F/V), (K/R), (Q/N), (D/E), and (G/A), and

combinations thereof.

26. The method of claim 16 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

27. The method of claim 16 comprising expressing a DNA encoding a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein and factor H, including in phase a DNA encoding at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, not including combinations consisting of complement receptor 1 and complement receptor 2.

28. The method of claim 16 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

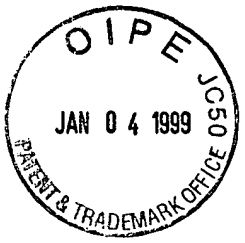
29. The method of claim 16 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

30. The method of claim 16 further comprising isolated the analog and mixing with the isolated analog a pharmaceutically acceptable carrier for administration to a patient in need thereof.

31. A DNA sequence which encodes an analog of claim 1.

32. The DNA sequence of claim 31 inserted into an expression vector operably linked to control sequences compatible with a host cell, which is capable, when transformed into the expression vector, of expressing a DNA encoding the analog of claim 1.

34. A method for enhancing the C4b or C3b cofactor activity of a complement regulatory protein, wherein the protein has either C3b or C4b cofactor activity, comprising adding sequences to the protein conferring binding of the other ligand, either C4b or C3b, wherein the sequences are present in a protein selected from the group of naturally occurring complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, not including combinations consisting of complement receptor 1 and complement receptor 2.



APPENDIX II: CLAIMS ON APPEAL AS PROPOSED TO BE AMENDED

1. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and those complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein said protein analog is selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b or C3b and C4b.

3. The analog of claim 1 wherein the protein is complement receptor one.

4. The analog of claim 1 wherein the protein is decay accelerating factor.

5. The analog of claim 1 wherein the protein is factor H.

8. An analog of a protein

selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to

amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; and substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), or these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G.

9. An analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13 selected from the group consisting of:
79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T

(amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37: S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), and these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G.

10. An analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of 180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No.

4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), and these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G.

11. The analog of claim 1 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

12. The analog of claim 1 comprising at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H.

13. The analog of claim 1 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

14. The analog of claim 1 wherein the region of the protein having biological activity consists of three short consensus regions and has two complement regulatory activities.

15. The analog of claim 1 further comprising a pharmaceutically acceptable carrier for administration to a patient in need thereof.

16. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these complement regulating proteins wherein the carboxy terminus is removed to allow the protein to be secreted, comprising

constructing a DNA sequence encoding a protein analog selected from the group consisting of complement regulating protein analogs containing short consensus repeats derived from a second, different complement regulating protein not including combinations consisting of complement receptor 1 and complement receptor 2, complement regulating protein analogs wherein the short consensus repeats are rearranged, and complement regulating protein analogs consisting of as few as three short consensus repeats, wherein the protein analog binds C3b, C4b, or C3b and C4b, and

expressing the DNA sequence in a suitable host for expression of the protein analog.

18. The method of claim 16 wherein the protein used to form the analog is complement receptor one.

19. The method of claim 16 wherein the protein is decay accelerating factor.

20. The method of claim 16 wherein the protein is factor H.

23. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid

substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

CR1-4 with its first 122 amino acids (SCR1-2) (Sequence ID Nos. 1 and 3) replaced with CR1 amino acids 497-618 (SCR 8-9) (Sequence ID Nos. 2 and 4) and CR1-4(8,9) with deletion of 194-253; substitution of amino acids 271-543 with: T-R-T-T-F-H-L-G-R-K-C-S-T-A-V-S-P-A-T-T-S-E-G-L-R-L-C-A-A-H-P-R-E-T-G-A-L-Q-P-P-H-V-K (Sequence ID No. 11), and these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G,

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

24. A method for making an analog of a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, factor H, and these proteins wherein the carboxy terminus is removed to allow the protein to be secreted, wherein the protein analog contains amino acid substitutions in the short consensus repeats which correspond to amino acid substitutions in the short consensus repeats of complement receptor one (SEQ ID No: 13) selected from the group consisting of:

79: D (amino acid 19 of Sequence ID No. 4); 37,79: Y,D (amino acid 37 of Sequence ID No. 2 and amino acid 19 of Sequence ID No. 4); 92: T (amino acid 32 of Sequence ID No. 4); 92-94: K...Y (amino acids 32-34 of Sequence ID NO. 3); 99,103,106: S...T...I (amino acids 39, 43 and 46 of Sequence ID No. 3); 109-112: D-T-V-I (amino acids 49-52 of Sequence ID No. 3); 110: T (amino acid 50 of Sequence ID No. 3); 111: V (amino acid 51 of Sequence ID No. 3); 112: I (amino acid 52 of Sequence ID No. 3); 1,3: Q...N (amino acids 1, 3 of Sequence ID No. 1); 6-9: E-W-L-P (amino acids 6-9 of Sequence ID No. 1); 12-16, 18-21: K-L-K-T-Q...N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 27,29: S...K (amino acids 27,29 of Sequence ID No. 2); 37: S (amino acid 37 of Sequence ID No. 1); 44, 47, 49: I...K...S (amino acids 44, 47, 49 of Sequence ID No. 1); 52-54, 57, 59: T-G-A...R...R (amino acids 52-54, 57, 59 of Sequence ID No. 1); 78-79, 82: K-G...F (amino acids 18-19, 22 of Sequence ID No. 3); 85, 87: Q...K (amino acids 25, 27 of Sequence ID No. 3); 12-16, 18-21: R-P-T-N-L...D-E-F-E (amino acids 12-21 of Sequence ID No. 1); 27,29: Y...N (amino acids 27, 29 of Sequence ID No. 1); 35, 64-65, 94: G...R-N...Y (amino acid 35 of Sequence ID No. 1, amino acids 4-5, 34 of Sequence ID No. 3), and these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G,

the method comprising expressing a DNA encoding the protein analog in a suitable host cell and recovering the protein analog.

25. A method for making an analog of decay accelerating factor wherein one or more substitutions are introduced into the region of the protein corresponding to decay accelerating factor short consensus repeats SCRs 2-3 as shown in Sequence ID No. 17 selected from the group consisting of

180-187: S-T-K-P-P-I-C-Q (amino acids 54-61 of Sequence ID No. 4); 175-178: N-A-A-H (amino acids 49-52 of Sequence ID No. 4); 175-187: S-T-K-P-P-I-C-Q-N-A-A-H (Sequence ID No. 9); 130: R (amino acid 4 of Sequence ID No. 3); 145: D (amino acid 19 of Sequence ID No. 4); 77-84: K-L-K-T-Q-T-N-A-S-D (amino acids 12-21 of Sequence ID No. 2); 90-92: S-L-K (amino acids 27-29 of Sequence ID No. 2), and these amino acid sequences where I is replaced with either L or V, L is replaced with either I or V, V is replaced with I, L, or F, F is replaced with V, K is replaced with R, R is replaced with K, Q is replaced with N, N is replaced with Q, D is replaced with E, E is replaced with D, G is replaced with A, or A is replaced with G.

26. The method of claim 16 wherein the complement regulatory protein is factor H comprising sequences conferring on the protein an activity selected from the group consisting of C3b binding activity, C3b cofactor activity, C4b binding activity, and C4b cofactor activity, wherein the sequences are derived from a protein selected from the group consisting of complement receptor 1, membrane cofactor protein, C4 binding protein, and factor H.

27. The method of claim 16 comprising expressing a DNA encoding a protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein and factor H, including in reading frame a

DNA encoding at least one short consensus repeat derived from a different protein selected from the group consisting of complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4 binding protein, and factor H, not including combinations consisting of complement receptor 1 and complement receptor 2.

28. The method of claim 16 wherein the protein analog includes SCRs 2, 3 and 4 of DAF and has C3b cofactor activity, C4b cofactor activity and decay accelerating activity.

29. The method of claim 16 wherein the protein consists essentially of three short consensus regions and has two complement regulatory activities.

30. The method of claim 16 further comprising isolated the analog and mixing with the isolated analog a pharmaceutically acceptable carrier for administration to a patient in need thereof.

31. A DNA sequence which encodes an analog of claim 1.

32. The DNA sequence of claim 31 inserted into an expression vector operably linked to control sequences compatible with a host cell, which expression vector is capable, when transformed into the host cell, of expressing a DNA encoding the analog of claim 1.

34. A method for enhancing the C4b or C3b cofactor activity of a complement regulatory protein, wherein the protein has either C3b or C4b cofactor activity, comprising adding sequences to the protein conferring binding of the other ligand, either C4b or C3b, wherein the sequences are present in a protein selected from the group of naturally occurring complement receptor 1, complement receptor 2, decay accelerating factor, membrane cofactor protein, C4

binding protein, and factor H, not including combinations consisting of complement receptor 1 and complement receptor 2.